REMARKS/ARGUMENTS

Favorable reconsideration and continued examination of the present application are respectfully requested.

In the Office Action of January 26, 2005, claims 5 - 11, 13, 15 - 17, and 20 - 27 were rejected and claims 1 - 4, 12, 14, 18, 19, 28, and 29 were withdrawn from consideration. In the present amendments to the claims of the application, claims 5 - 8 and 10 - 11 are canceled, claims 9, 13, 15 - 17, 20, and 25 are amended and new claims 30 - 31 are added. The amendments to claims 9, 13, 15 - 17, and 25 are limited to a change in dependency, and the amendment to claim 20, by specifying cell-free protein synthesis, directs the claim to what the Examiner has deemed to be the elected subject matter. New claims 30 - 31 combine the subject matter of canceled claims 10 - 11 with steps of protein synthesis as in claim 20. Accordingly, no questions of new matter should arise, and entry of the amendment is respectfully requested.

Priority Document

At page 2 of the Office Action, the Examiner acknowledged Applicants' claim for foreign priority under 35 U.S.C. 119(a)-(d), but indicated that Applicants have not filed certified copy of the Japan 2001-016746. The Examiner is reminded that the present application was filed as National Phase application under 35 U.S.C. 371 and that accordingly, the priority document should be obtained by the Examiner directly from the International Bureau. The Examiner is respectfully requested to update the U.S. Patent and Trademark Office records and acknowledge receipt.

Objection to the Disclosure

At page 3 of the Office Action, the Examiner objected to the specification on the alleged grounds that the sequence at page 18, line 2, (SEQ ID NO:8) has 20 nucleotides, and therefore is not consistent with the sequence listing, which shows SEQ ID NO:8 as having 19 nucleotides. (The Examiner's statement contains an error in that the actual nucleotide numbers are 30 and 29, respectively.) In response, the sequence of page 18, line 2 is corrected to delete the G in position 12, so that the SEQ ID NO:8 provided on page 18, line 2 is identical to the SEQ ID NO:8 in the sequence listing. Accordingly, the objection should be withdrawn.

Formal Drawings

At page 4 of the Office Action, the Examiner acknowledged the proposed drawings of Fig. 3 and 8 filed on July 18, 2002 and requested a complete set of formal drawings. A complete set of formal drawings is submitted herewith as a separate paper.

Objection to claims 5, 6, 10, 11, 13, 15 and 20 - 25

At page 4 of the Office Action, the Examiner objected to claims 5, 6, 10, 11, 13, 15, and 20 - 25 on the alleged grounds that they contain recitation of a non-elected invention, protein synthesis in a cell. This objection is moot with respect to claims 5, 6, 10, and 11, which have been canceled. Independent claim 20 is amended to specify a cell-free protein synthesis system, and claims 13 and 15 are amended to ultimately depend from claim 20. Moreover, new claims 30 and 31 specify a cell-free protein system. Accordingly, the objection is overcome.

Objection to claims 6, 10, 11, 13, and 15

Also at page 4 of the Office Action, the Examiner objects to claims 6, 10, 11, 13, and 15, because of the use of "Sequence Nos." instead of "SEQ ID NO:" to refer to sequences in the sequence listing. This objection is moot with respect to claims 6, 10, and 11, which have been canceled. Claims 13 and 15 are amended to depend from claim 21, which uses the term "SEQ ID NO:" and this term is used in new claims 30 and 31, which replace original claims 10 and 11. Accordingly, the objection is overcome.

Rejection of claims 5 - 11, 13, 15 - 17, 20, 21, 24, 26, and 27 under U.S.C. §112, first paragraph- written description

Also at page 4 of the Office Action, the Examiner rejected claims 5 - 11, 13, 15 - 17, 20, 21, 24, 26, and 27 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. In the detailed comments on pages 4 - 8 of the Office Action, the Examiner took the position that while the specification provides a written description of the RNA higher-order structure that contains one of the sequences of SEQ ID NO: 1 - 7 or a sequence containing a mutation of PKI in the PSIV-IRES to permit translation of a GFP gene, the specification does not provide a written description of the genus of variants for an RNA higher-order structure with PK I, II and III structures and a function of promoting translation activity, or a RNA higher-order structure made up of a base sequence having at least about 50% homology to the sequence of SEQ ID NO: 1 - 6 or 7, a complementary strand of the base sequence, a sequence hybridizing to the base sequence under stringent condition or a base sequence that has been

mutated or altered. For the following reasons, the rejection is respectfully traversed.

In the broadest aspects, the present invention relates to a method for synthesizing a heterologous protein in which the cell-free protein expressing system includes a polynucleotide that promotes translation activity. The polynucleotide that promotes translation activity is further defined in the claims by having an RNA higher-order structure including PK (pseudoknot) I, II, and III structures. The present specification contains a thorough explanation of what is meant by an RNA higher-order structure including PK (pseudoknot) I, II, and III structures, particularly in Example 1 at pages 14 - 15 and Figures 5 - 6 of the present specification. The genus of polynucleotides that contain the RNA higher-order structure including PK (pseudoknot) I, II, and III structures is thoroughly described on pages 4 - 8 of the present specification. Accordingly, the Examiner is clearly in error in alleging that the present specification does not disclose a genus of variants for the RNA higher order structure and in alleging that the subject matter is not described in the present specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention.

Further, with respect to the specific invention claimed herein, the Examiner is clearly in error in asserting that the written description requirement requires a teaching of all of the possible nucleotide sequences for the RNA structures according to the present invention. The particular case law cited by the Examiner is not on point and is clearly distinguished from the facts of the present invention. Specifically, *Fiers*, *Amgen*, and *Fiddes* each specifically relate to the adequacy of conception or written description for claimed DNA that encodes a specific protein. For example, in *Fiers v. Revel*, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993), the issue considered by the

court was whether any of the parties could show conception and reduction to practice of DNA coding for a specific interferon, b-IF and the court found that conception required that a party set forth the complete nucleotide sequence of the DNA coding for the protein. In *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.,* 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991), the issue considered by the court was whether one of the parties could show conception and reduction to practice of DNA coding for a human EPO, and the court found that the party could not have conceived of the complete sequence of DNA coding for human EPO, since the amino acid sequence of human EPO was not known with certainty at the alleged date of conception. In *Fiddes v. Baird,* 30 U.S.P.Q.2d (Fed. Cir. 1993), the issue considered by the court was whether a written description of a theoretical DNA sequence encoding bovine pituitary FGF provided support for the class of DNAs encoding all mammalian FGFs. The court found that since there was no written description of a broad class of mammalian FGFs, there was no support for a claim to DNAs encoding mammalian FGFs. In other words, each of these cases are clearly limited by their particular facts, that the claims in issue related to a DNA encoding a specific protein or specific class of proteins.

In the present invention, on the other hand, the polynucleotide that the Examiner alleged lacks written description is not a polynucleotide encoding a protein, but rather is a molecule that accomplishes a physical result, the initiation of transcription, based on its physical structure, the presence of a RNA higher order structure including PK (pseudoknot) I, II, and III structures. Unlike a coding sequence, in which a specific sequence is absolutely required in order to encode a specific protein, the present invention clearly relates to a structure in which absolute specificity

of each nucleotide is not required In other words, the present invention may be considered analogous to a mechanical invention in that the overall structural details are more important than the exact identity of the individual parts. As discussed above, the RNA higher order structure that accomplishes the result is thoroughly described in the specification. Moreover, persons skilled in the art, and with knowledge of the basic principles of RNA base pair formation, can readily envision alterations that could be made in the structures described in Figures 5 and 6 and in sequences of SEQ ID NO: 1-7 or their complementary sequences that would retain the higher order structure. Accordingly, the present specification provides a written description of the claimed invention, and the rejection should be withdrawn.

Rejection of claims 5 - 11, 13, 15 - 17, and 20 - 25 under U.S.C. §112, second paragraph-indefiniteness

At page 8 of the Office Action, the Examiner rejected claims 5 - 11, 13, 15 - 17, and 20 - 25 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

Regarding claims 5 - 11, 13, and 15 - 17, the Examiner alleged that these claims are indefinite because they lack essential steps in the method of synthesizing a heterologous polypeptide and that the missing steps are the system for protein expression and the translation step. This rejection is moot with respect to claims 5 - 11, which are canceled herein. Claims 13, 15, and 17 are amended to ultimately depend from claim 20, which includes the steps in the method of synthesizing a heterologous protein or polypeptide.

Regarding claims 6, 10, 11, 13, 15, and 21, the Examiner alleged that these claims are

indefinite because the use of the term "a base sequence hybridizing with the base sequences of 1) to 4) under stringent conditions" does not specify the conditions of hybridization and does not specify what sequence the hybridized nucleotide has. This rejection is moot with respect to claims 6, 10, and 11, which are canceled herein. For the following reasons, the rejection is traversed as it may be applied to claims 13, 15, and 21, as well as new claims 30 and 31. The stringent hybridization conditions are defined on page 9 of the present specification. Accordingly, persons skilled in the art upon reading the present specification would clearly know what conditions are required for hybridization. Moreover, as discussed above, the nature of the present invention is such that it is not crucial to know exactly what the nucleotide sequence is obtained by hybridization, since the polynucleotide that has a function of promoting translation is not a coding sequence. All that is necessary is that the polynucleotide have the higher order structure as clearly defined in the present specification.

Regarding claims 10 and 11, the Examiner alleged that these claims are indefinite as to the term "the sequence including a base sequence." This rejection is moot because claims 10 and 11 are canceled herein. New claims 30 and 31 do not contain the term "the sequence including a base sequence," and accordingly the rejection is overcome with respect to these claims

Regarding claims 20 - 25, the Examiner alleged that these claims are indefinite for failing to specify what protein expression system is provided for synthesizing a heterologous polypeptide. In response, the claims are clearly definite. To assist the Examiner, claims 20 - 25 specify that protein synthesis occurs in a cell-free system.

Regarding claim 25, the Examiner alleged that there is insufficient basis for the limitation

of lines 3 - 4 in claim 22, since claim 22 does not recite a mutation in the base sequence. In response, this rejection is overcome by the amendment to claim 25 to depend from claim 20 instead of from claim 22.

Accordingly, it is respectfully submitted that all of the rejections under 35 U.S.C. §112, second paragraph, for indefiniteness should be withdrawn.

Rejection of claims 5 - 7, 9, 13, 15, 16, 20 - 23, and 26 under 35 U.S.C. §102(b) as anticipated by Sasaki et al.

At page 9 of the Office Action, the Examiner rejected claims 5 - 7, 9, 13, 15, 16, 20 - 23, and 26 under 35 U.S.C. § 102(b) as being anticipated by Sasaki et al (J. Virology, 73, 1219-1226 (1999)). The Examiner alleges that Sasaki et al. teaches AUG-unrelated translation initiation that is mediated by the IRES of PSIV *in vitro*. The Examiner further alleges that Sasaki et al. teaches that the LUC gene (a heterologous protein) was translated when fused downstream of $IRES_{6201}$ or $IRES_{6264}$ and that $IRES_{6264}$ contains SEQ ID NO:1. Further, the Examiner alleges that $IRES_{6201}$ has at least 50% homology to SEQ ID NO:1. The Examiner notes that Sasaki et al. does not specifically indicate that the IRES sequences have an RNA higher order, but the Examiner takes the position that the sequences would be expected to have at least the PK I, II or III structure, since $IRES_{6264}$ contains SEQ ID NO:1. Accordingly, the Examiner views the Sasaki et al. reference as disclosing a species that anticipates the invention. For the following reasons, this rejection is traversed.

Sasaki et al. confirms only the translation of a virus coat protein and luciferase genes as a

fusion protein. As shown in the lanes 2 and 3 in Fig. 5, no protein synthesis via IRES was found in IRES6192-Luc and IRES6195-Luc. The abstract in the article states that the 3' terminus of IRES overlaps with the coat protein coding region only in a little part. The article brings an opposite result to the present invention. It is because restriction enzyme (BamHI) was employed at that time to ligate IRES with luciferase gene so that a recognition sequence for the restriction enzyme might inhibit formation of the IRES higher-order structure to make it impossible to translate downstream immediately from PKI. Although a BamHI sequence is not described in Fig. 5, it is stated in the specification of a method for construction of the plasmid used in the experiment that BamHI was used to ligate (in the line 14 from the bottom, left column, page 1220). One important difference between the cited reference and the present invention is the finding that the structures of PKI, PKII, and PKIII can be maintained to allow synthesis of a heterologous protein immediately from a codon following PKI even if a fusion gene part (nucleotide No. 6193-6201 in PSIV) of the virus coat protein gene is absent, resulting in bringing about an industrial applicability.

Although the IRES higher order structure consisting of PKI, PKII, and PKIII is reserved in every virus, the reserved structure could not be found in the coat protein coding region of every virus. Thus, the present inventors doubted the previous data that translation via IRES needed the coat protein coding region (Fig. 5 in the cited reference), and attempted translation of a gene with the coat protein coding region deleted. The present inventors found that the translation was successful, thereby to complete the present invention. Fig. 5 in the cited reference does not anticipate the present invention, and actually teaches away by indicating that it

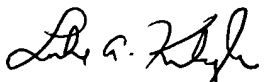
is impossible to synthesize a protein starting with an arbitrary amino acid. In other words, Fig. 5 suggests that protein synthesis using IRES needs the virus coat protein of the N-terminal portion. Furthermore, the cited reference can not anticipate the present invention because it lacks awareness of the existence of PKII and PKIII.

For these reasons, the rejection should be withdrawn.

Conclusion

If there are any other fees due in connection with the filing of this response, please charge the fees to Deposit Account No. 50-0925. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such extension is requested and should also be charged to said Deposit Account.

Respectfully submitted,



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